PCT/GB2004/050046

PA 1259667

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 14, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/532,370***
FILING DATE: ***December 24, 2003***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.	ER 013886601 US

Inventor(s)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Matthew	Fyfe	Oxford, UK
Lisa	Gardner	Oxford, UK
John	King-Underwood	Oxford, UK

4 Additional Inventors are being named on the 1 separately numbered sheet attached hereto

Title of the Invention (500 characters max)
GPCR RECEPTOR AGONISTS

CORRESPONDANCE ADDRESS					
Direct all correspondence to:					
Firm Name	OSI Pharmaceuticals, Inc.				
Address	Patent Department				
Address	58 South Service Road, Suite 110				
City	Melville	State	New York	Zip	11747
Country	U.S.A.	Telephone	(631)962-2000	Fax	(631)752-3880

ENCLOSED APPLICATION PARTS (Check all that apply)		
X	Specification	Number of Pages: 40
	Drawing(s)	Number of Sheets: 0
	Application Data Sheet	
	CD(s)	Number: 0
X	Return Postcard	
X	Other (specify)	Check #025516 for $160.00 filing fee

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT		
X	A check or money order is enclosed to cover the filing fees	
	The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:	502783
	Filing Fee Amount ($)	$160.00

This invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. (NO) **, the name of the U.S. Government agency and the Government contract number are:** _____

Respectfully submitted, Date Dec. 24, 2003

SIGNATURE Kim T. Nguyen Registration No. 47,821
Typed or Printed Name: Kim T. Nguyen
Telephone: (631) 962-2089
Docket No.: NC-10009PV

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION FOR PATENT COVER SHEET
Additional Page

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.	**ER 013886601 US**

Docket Number:	NC-10009PV

Inventor(s)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Martin	Procter	Oxford, UK
Chrystelle	Rasamison	Oxford, UK
Karen	Schofield	Oxford, UK
Gerard	Thomas	Oxford, UK

Title of the Invention (500 characters max)
GPCR RECEPTOR AGONISTS

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Number 2 of 2 pages

Docket No. OS-10009-PV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Fyfe, M. et al.
Serial No.:	Not yet known
Filed:	Herewith
Title:	GPCR Receptor Agonists

December 24, 2003

BY EXPRESS MAIL
MAIL STOP PROVISIONAL PATENT APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

EXPRESS MAIL CERTIFICATE OF MAILING
FOR THE ABOVE-IDENTIFIED APPLICATION

"Express Mail" mailing label number: ER 013886601 US
Date of Deposit: December 24, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By Kim T. Nguyen Printed name Kim T. Nguyen

Very truly yours,

Kim T. Nguyen

Kim T. Nguyen
Agent for Applicant
Registration No. 47,821
Telephone No. (631) 962-2089
Fax No. (631) 752-3880

December 24, 2003
OSI Pharmaceuticals, Inc.
58 South Service Road, Suite 110
Melville, NY 11747

TITLE OF THE INVENTION

GPCR RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to agonists of GPR116 that are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

Obesity is characterized by an increase in adipose tissue mass. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)^2), or waist circumference. Individuals are considered obese when the BMI is greater than 30. It has been an accepted medical view for some time that an increased body weight, especially abdominal body fat, is associated with increased risk for diabetes, hypertension, heart disease, and numerous other health complications such as arthritis, stroke, gallbladder disease, muscular and respiratory problems and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. leptin, insulin, neuropeptide Y, ghrelin, and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight, such as insulin and leptin, and adipose tissue derived peptides.

Insulin dependent Type I diabetes and non-insulin dependent Type II diabetes continue to present treatment difficulties even though clinically accepted regimens that include diet, exercise, hypoglycemic agents, and insulin are available. Treatment is patient dependent, therefore there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, hypertension and its associated pathologies such as, for example, atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with elevated insulin levels (hyperinsulinemia), which can lead to abnormal blood sugar levels. Furthermore, myocardial ischemia can result.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR116 is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, U.S. Pat. No. 6,468,756 also discloses the mouse receptor.

In humans GPR116 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR116 receptor indicates it's potential utility as a target for the treatment of obesity and diabetes.

Williams J.P., Combinatorial Chemistry & High Throughput Screening, 2000, 3, 43-50 discloses the compounds 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine and 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ^{t}butyl ester, synthesized as part of a compound library designed to identify dopamine D_4 ligands.

The compounds 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine and 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chem Div) and 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chembridge) are / were commercially available, no pharmaceutical utility has been suggested for these compounds.

The present invention relates to agonists of GPR116 which are useful as peripheral regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

SUMMARY OF THE INVENTION

Compounds of formula (I):

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. in the prophylactic or therapeutic treatment of obesity, and for the treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

wherein V is a 5-membered heteroaryl ring comprising up to four heteroatoms selected from O, N and S;

A is $(CH_2)_n$;

B is $(CH_2)_n$, wherein one of the CH_2 groups is optionally replaced by O, NR^5, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

R^1 is 3- or 4-pyridyl or 4- or 5-pyrimidinyl any of which is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, aryl, OR^6, CN, NO_2, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

R^2 is a 4- to 7-membered cycloalkyl substituted by R^3, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or a 4- to 7-membered heterocyclyl containing one or two nitrogen atoms which are unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$ or $S(O)_2R^3$;

R^3 is C_{3-7} alkyl, C_{3-7} alkenyl or C_{3-7} alkynyl wherein one of the CH_2 groups is optionally replaced by O, C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^4 is C_{2-7} alkyl, C_{2-7} alkenyl or C_{2-7} alkynyl wherein one of the CH_2 groups is optionally replaced by O, or C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^5 is hydrogen, $C(O)R^7$, $S(O)_2R^8$ or C_{1-4} alkyl optionally substituted by OR^6, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups are optionally substituted with one or more substituents selected from halo, C_{1-2} alkyl, C_{1-2} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^6 are independently hydrogen, or C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocyclyl group or heteroaryl, wherein the cyclic groups are optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^9, CN, SO_2CH_2, $N(R^{10})_2$, and NO_2; or a group $N(R^{10})_2$ optionally forms a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR^{10};

R^7 is hydrogen, C_{1-4} alkyl, OR^6, $N(R^6)_2$, aryl or heteroaryl;

R^8 is C_{1-4} alkyl, C_{1-4} fluoroalkyl, aryl or heteroaryl;

R^9 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl; and

R^{10} is hydrogen or C_{1-4} alkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ^{t}butyl ester;

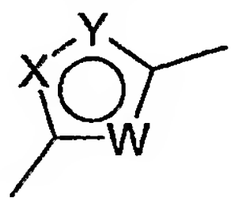
c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600.

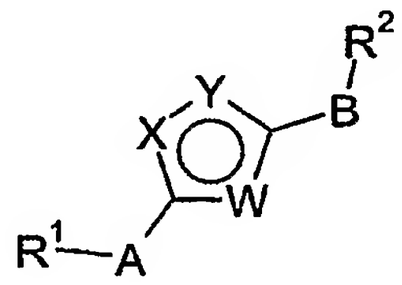
In the compounds of formula (I) V may represent a 5-membered heteroaryl ring containing up to three heteroatoms selected from O, N and S of the formula:



Preferably n is independently 0, 1 or 2.

R^2 is preferably a 4- to 7-membered cycloalkyl substituted by R^3, or 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by $C(O)OR^4$.

A specific group of compounds of the invention which may be mentioned are those of formula (Ia), or a pharmaceutically acceptable salt thereof:



(Ia)

wherein two of W, X and Y are N, and the other is O;

A is $(CH_2)_n$;

B is $(CH_2)_n$, wherein one of the CH_2 groups is optionally replaced by O, NR^5, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

R^1 is 3- or 4-pyridyl or 4-pyrimidinyl any of which is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-7} cycloalkyl, OR^5, CN, NO_2, $N(R^6)_2$, $CON(R^6)_2$ or a 5- or 6-membered heteroaryl group;

R^2 is 4- to 7-membered cycloalkyl substituted by R^3, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or 4- to 7-membered heterocyclyl containing one or two nitrogen atoms which is unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$ or $S(O)_2R^3$;

R^3 is C_{3-7} alkyl, C_{3-7} alkenyl or C_{3-7} alkynyl wherein one of the CH_2 groups is optionally replaced by O, or C_{3-7} cycloalkyl, aryl or C_{1-4} alkylaryl, wherein the aryl groups is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6a}, CN, $N(R^{6b})_2$ and NO_2;

R^4 is C_{2-7} alkyl, C_{2-7} alkenyl or C_{2-7} alkynyl wherein one of the CH_2 groups is optionally replaced by O, or C_{3-7} cycloalkyl, aryl or C_{1-4} alkylaryl, wherein the aryl groups is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6a}, CN, $N(R^{6b})_2$ and NO_2;

R^5 is hydrogen or C_{1-4} alkyl;

R^{6a} is hydrogen, C_{1-4} alkyl or C_{1-4} fluoroalkyl; and

R^{6b} are independently hydrogen and C_{1-4} alkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ^{t}butyl ester;

c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl,

heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term "fluoroalkyl" includes alkyl groups substituted by one or more fluorine atoms, e.g. CH_2F, CHF_2 and CF_3.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes monocyclic saturated carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "halo" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" includes phenyl and naphthyl, in particular phenyl.

Unless otherwise indicated the term "heterocyclyl" and "heterocyclic ring" includes 4- to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Examples of heterocyclic rings that R^2 may represent include azetidine, pyrrolidine, piperidine and piperazine. R^2 heterocyclyl groups may also contain additional heteroatoms, e.g. morpholine.

Unless otherwise stated, the term "heteroaryl" includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline and purine.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes

all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

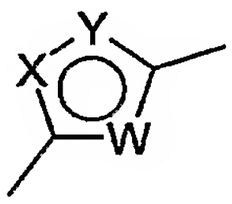
When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N*′,*N*′-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below, in which, for illustrative purposes, -V- is shown as a group of the formula:

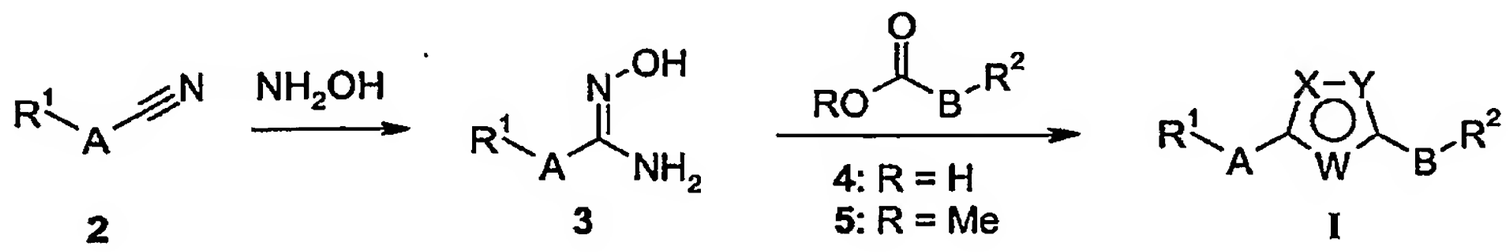


and R^1, R^2, R^3, R^4, A, B, W, X and Y are as defined above.

The compounds of formula (I), in which X = N, Y = O and W = N, may be prepared according to the method illustrated in Scheme 1. The nitriles of formula **2** are either commercially available or can be synthesized using known techniques. Compounds of formula **2** are treated with hydroxylamine in a suitable solvent, such as ethanol-water, at elevated temperature, to afford amidoximes of formula **3** (synthesis of amidoximes is further described by A. R. Martin et al, J. Med. Chem., 2001, 44, 1560). Compounds of formula **3** are subsequently condensed with acids of formula **4**, which are themselves either commercially available or can be readily synthesized using known techniques. The condensation firstly entails activation of compounds of formula **4** by, for example, formation of the mixed anhydride, in which the acid is treated with a chloroformate, such as isobutylchloroformate, in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as THF or toluene, followed by addition of compounds of formula **3**. Alternatively, compounds of formula **4** may be activated by conversion to the acid halide, generated by treatment of the acid with, for example, oxalyl chloride in a suitable solvent, such as CH_2Cl_2-DMF. The intermediates arising from the condensation of amidoximes of formula **3** and acids of formula **4** are dissolved

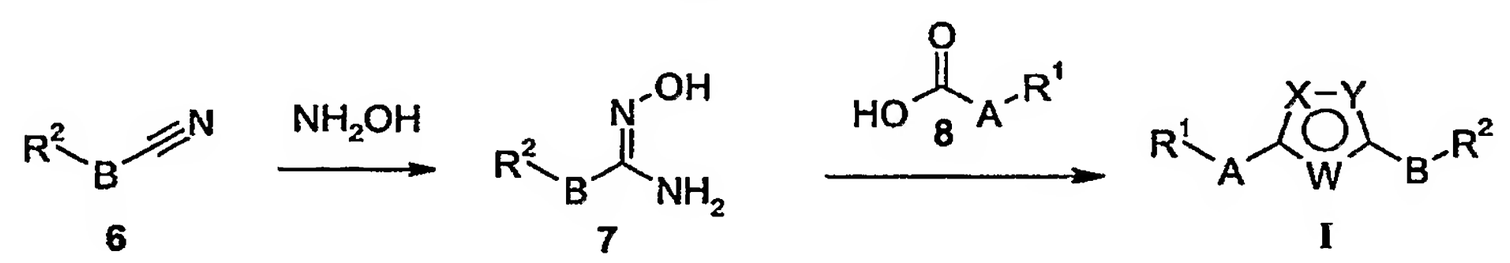
in an appropriate solvent, such as toluene or xylene, and heated under reflux, with concomitant removal of water by Dean-Stark apparatus or by molecular sieves, to form oxadiazoles of formula (I). Alternatively, amidoximes of formula **3** can firstly be treated with a suitable base, for example sodium hydride, in an appropriate solvent, such as THF, and subsequently esters of formula **5**. Heating of this mixture also generates oxadiazoles of formula (I) (this process is further illustrated by R. H. Mach et al, Bioorg. Med. Chem., 2001, 9, 3113).

Scheme 1



Compounds of formula (I) in which X = O, Y = N and W = N may be prepared according to the method outlined in Scheme 2. The nitriles of formula **6** are either commercially available or can be synthesized using known techniques. These are converted to the corresponding amidoximes of formula **7**, as described above, and subsequently condensed with acids of formula **8**, which are commercially available or can readily be synthesized by those skilled in the art. This condensation is performed in a fashion analogous to that described in Scheme 1, to afford the corresponding oxadiazoles of formula (I).

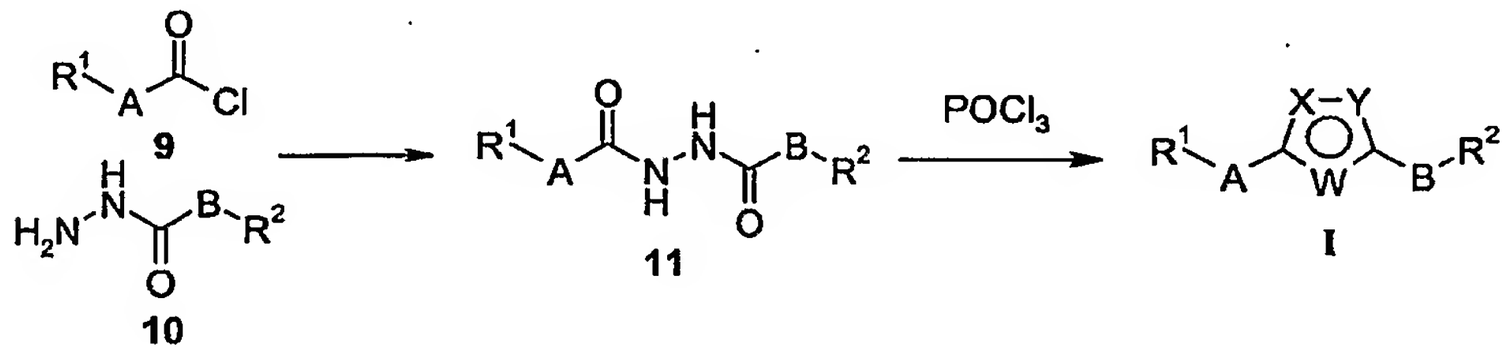
Scheme 2



Compounds of formula (I) in which X = N, Y = N and W = O can be synthesized as outlined in Scheme 3. The acyl chlorides of formula **9** are either commercially available or may be synthesized using known methods. The acid hydrazides of formula **10** can be readily obtained by, for example, treating an ethanolic solution of the corresponding ester with hydrazine (for further details see K. M. Kahn et al, Bioorg. Med. Chem., 2003, 11, 1381). Treating the acyl chlorides of formula **9** with the acid hydrazides of formula **10** in a suitable solvent, such as pyridine, affords compounds of

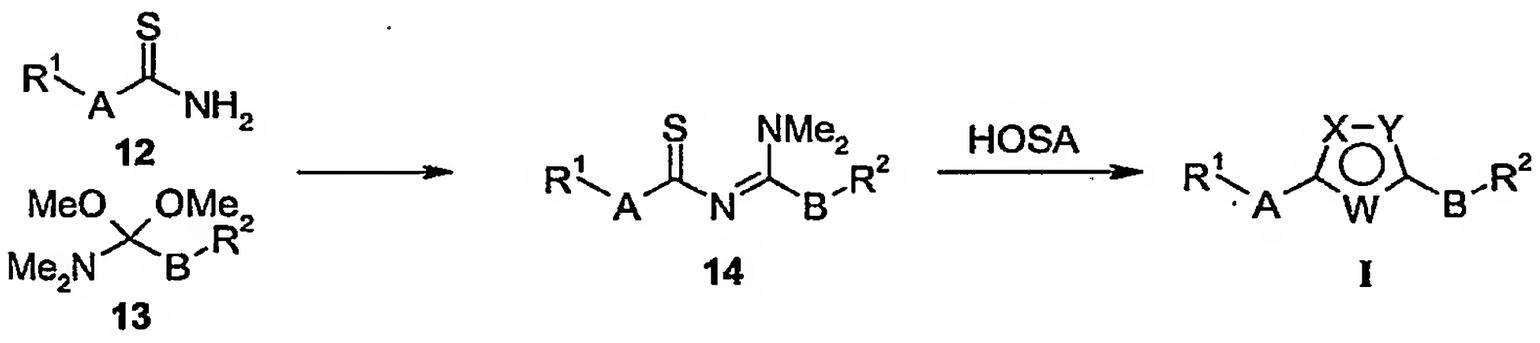
formula **11** (further illustrated by V. N. Kerr et al, J. Am. Chem. Soc., 1960, 82, 186), which are then converted by $POCl_3$ at elevated temperature to compounds of formula (I) (this process is further described by S-A. Chen et al, J. Am. Chem. Soc., 2001, 123, 2296).

Scheme 3



Compounds of formula (I) where X = S, Y = N and W = N can be formed from compounds of formula **12** (Scheme 4) which are commercially available, or can be readily synthesized from the corresponding carbonyl compound and Lawesson's reagent under standard conditions. Treating á compound of formula **12** with a compound of formula **13** in a suitable solvent such as dichloromethane at about 20°C gives compounds of formula **14**. Compounds of formula **13** can be obtained by treating the corresponding dimethylamide with Meerwein's reagent (for details see M. Brown US 3,092,637). Compounds of formula **14** are then cyclised using hydroxylamine-*O*-sulfonic acid in the presence of a base, such as pyridine, in a suitable solvent such as methanol (for further details, see A. MacLeod et al, J. Med. Chem., 1990, 33, 2052).

Scheme 4

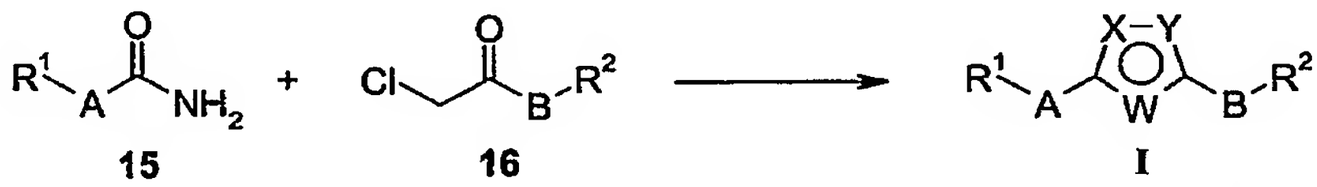


The regioisomeric derivatives of formula (I), where X = N, Y = S and W = N, can be formed in a similar manner by reversing the functionality of the reactants so the R^1 fragment contains the acetal moiety and the R^2 fragment contains the thiocarbonyl.

Compounds of formula (I) where W = O, X = N and Y = CH can be formed from compounds of formula **15** (Scheme 5). Compounds of formula **15** are commercially available or synthesized using known techniques. Chlorides of formula **16**

are commercially available, or can readily be formed by chlorinating the corresponding ketone using standard conditions, for example, bubbling chlorine gas through a methanol solution of the ketone (for further details see R. Gallucci & R. Going, J. Org. Chem., 1981, 46, 2532). Mixing a compound of formula **15** with a chloride of formula **16** in a suitable solvent, such as toluene, with heating, for instance at about 100°C gives compounds of formula (I) (for further information, see A. Hassner et al, Tetrahedron, 1989, 45, 6249). Compounds of formula (I) where W = O, X = CH and Y = N can be formed is a similar fashion by reversing the functionality of the reactants so the R^1 fragment contains the haloketone moiety and the R^2 fragment contains the $C(O)NH_2$.

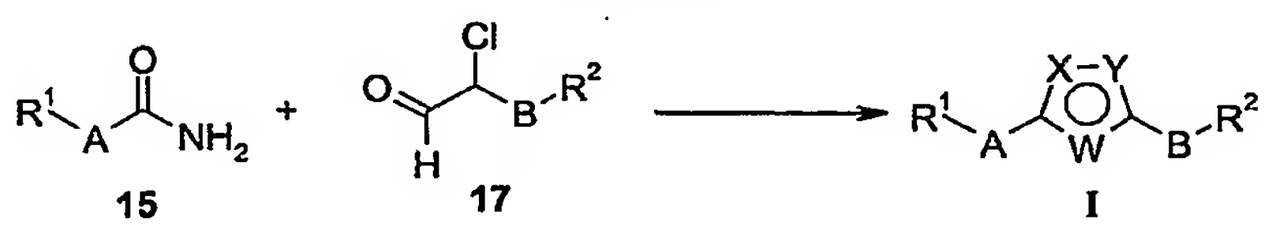
Scheme 5



Alternatively, compounds of formula (I) where X = S, W = N and Y = CH can also be formed from compounds of formula **16**. Heating an compound of formula **15** with phosphorus pentasulfide, followed by the addition of a compound of formula **16** followed by further heating gives compounds of formula (I) (for further details, see R. Kurkjy & E. Brown, J. Am. Chem. Soc., 1952, 74, 5778). The regioisomeric compounds where X = CH, W = N and Y = S can be formed is a similar fashion by reversing the functionality of the reactants, so the R^1 fragment contains the haloketone moiety and the R^2 fragment contains the $C(O)NH_2$.

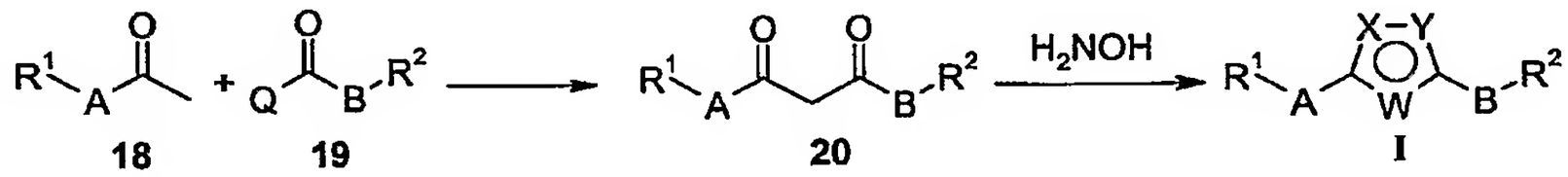
Compounds of formula I where W = N, X = O and Y = CH can be formed from compounds of formula **15** and formula **17** (Scheme 6) under similar conditions to those outlined for Scheme 5. Compounds of formula I where W = S, X = N and Y = CH can also be formed from compounds of formula **15** and formula **17** using the conditions involving phosphorus pentasulfide described above.

Scheme 6



Compounds of formula (I) where X = O, Y = N and W = CH, and where X = N, Y = O and W = CH and can be formed from compounds of formula **20** (Scheme 7). Acylation of compounds of formula **18** with a compound of formula **19**, where Q is alkoxide or chloride, can occur under standard conditions, for example, deprotonation of ketone **18** with a suitable base, such as lithium diisopropylamide or potassium ethoxide, in a suitable solvent, such as tetrahydrofuran, generally at low temperature. Treatment of compounds of formula **20** with hydroxylamine, in a suitable solvent, such as ethanol, at elevated temperature, for example 75°C, yields compounds of formula (I) as a mixture of both regioisomers of the isoxazole. Using standard separation techniques, such as chromatography on silica gel, the individual isomers can be isolated (for further details, see M. Rowley et al, J. Med. Chem., 1997, 40, 2374).

Scheme 7



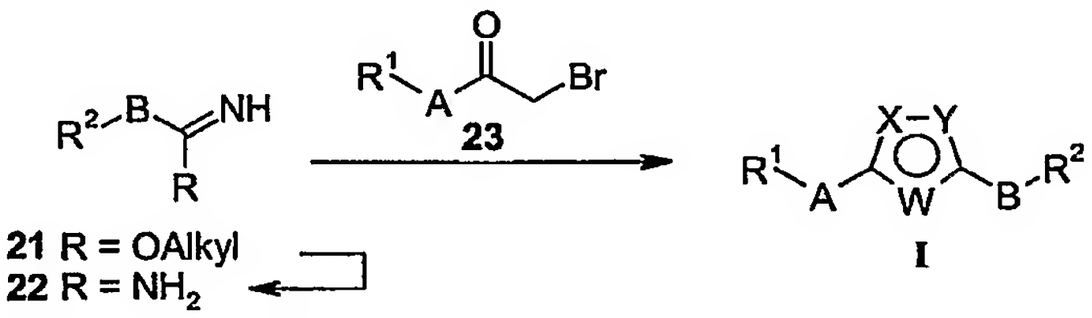
Compounds of formula (I) where X = S, Y = N and W = CH can be formed by hydrogenation of a compound of formula (I) where X = O, Y = N and W = CH, with platinum oxide in a suitable solvent such as ethanol, followed by heating with phosphorus pentasulfide to give compounds of formula (I) where X = S, Y = N and W = CH (for further details, see G. Wiegand et al, J. Med. Chem., 1971, 14, 1015). For details of the synthesis of the regioisomer where X = N, Y = S and W = CH also see G. Wiegand *ibid*).

Compounds of formula (I) where X = N, Y = N and W = CH can be formed from compounds of formula **20**. Treatment of compounds of formula **20** with hydrazine in a suitable solvent, such as methanol, would give rise to compounds of formula (I) where X = N, Y = N and W = CH (this process is further illustrated by R. Baker et al, J. Med. Chem., 1997, 40, 2374).

Compounds of formula (I) in which X = CH, Y = N and W = N can be synthesized as described in Scheme 8. Bromides of formula **23** are either commercially available or may be synthesized from the corresponding ketone by, for example, treating an aqueous solution of the ketone with Br_2 and HBr (as described by J. Y. Becker et al, Tetrahedron Lett., 2001, 42, 1571). The amidines of formula **22** may be synthesized by known methods, for example by treatment of the corresponding alkyl imidates of

formula **21** with ammonia in a suitable solvent, such as ethanol (as detailed by D. A. Pearson et al, J. Med. Chem., 1996, 39, 1372). The imidates of formula **21** may in turn be generated by, for example, treatment of the corresponding nitrile with HCl in a suitable solvent, such as methanol (for further details see J. P. Lokensgard et al, J. Org. Chem., 1985, 50, 5609). Reaction of amidines of formula **22** with bromides of formula **23** in a suitable solvent, such as DMF, affords compounds of formula (I) (illustrated by N. J. Liverton et al, J. Med. Chem., 1999, 42, 2180).

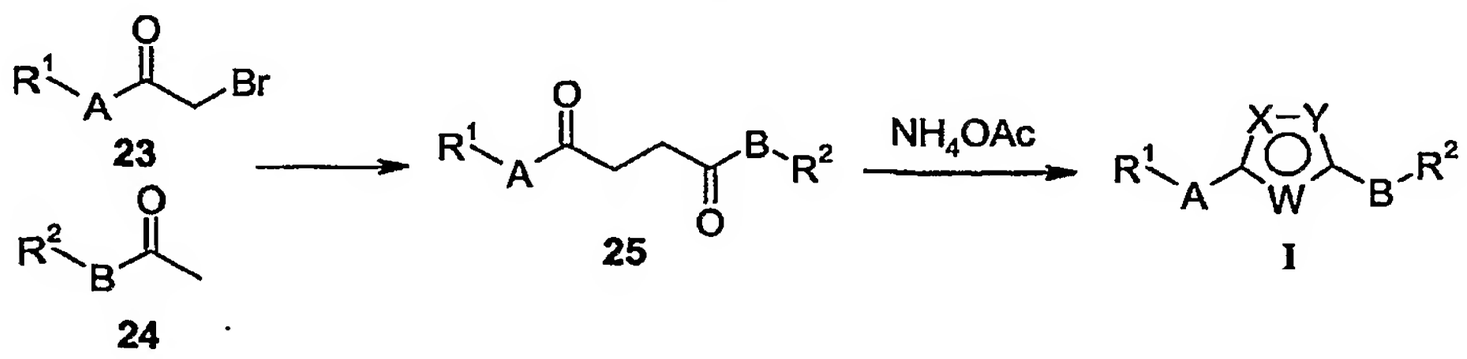
Scheme 8



The regioisomeric compounds where X = N, Y = CH and W = N can be formed in a similar fashion by reversing the functionality of the reactants, so the R^1 fragment contains the amidine moiety and the R^2 fragment contains the bromide.

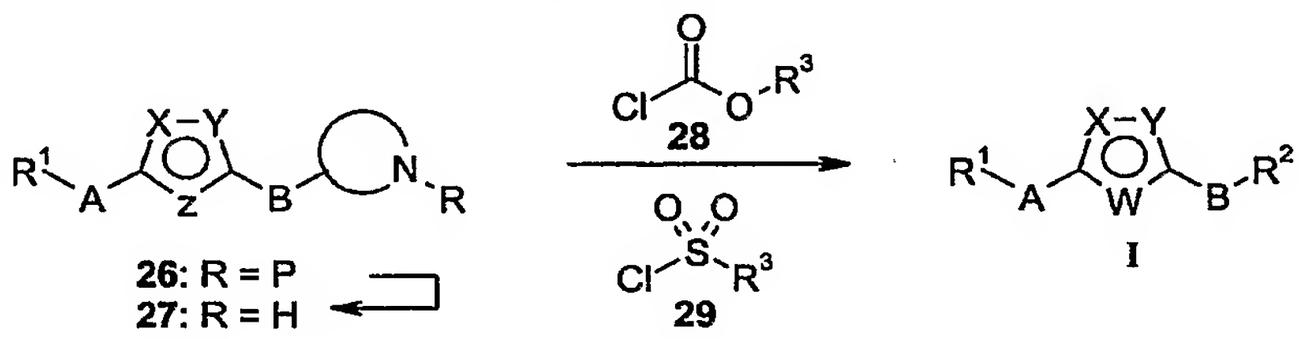
Compounds of formula (I) in which X = CH, Y = CH and W = N can be synthesized as illustrated in Scheme 9. Diketones of formula **25** are readily accessible by, for example, the condensation of ketones of formula **24**, which are commercially available or are readily synthesized using known techniques, with bromides of formula **23** in a suitable solvent, such as benzene using an appropriate catalyst. Illustrative examples are described by O. G. Kulinkovich et al, Synthesis, 2000, 9, 1259. Using a Paal-Knorr reaction, diketones of formula **25** may be treated with, for example, ammonium carbonate in a suitable solvent, such as ethanol at elevated temperature (for further details see R. A. Jones et al, Tetrahedron, 1996, 52, 8707) to afford compounds of formula (I).

Scheme 9



Compounds of formula (I) in which R^2 contains either a carbamate or a sulfonamide group may be synthesized as described in Scheme 10. Compounds of formula **26**, in which P represents a suitable protecting group, for example *tert*-butoxycarbonyl (Boc), may be synthesized as outlined in Schemes 1-9 above. The protecting group is firstly removed under suitable conditions to afford compounds of formula **27**. In the case of the Boc group this can be achieved by treatment of compounds of formula **26** with a suitable acid, such as trifluoroacetic acid, in an appropriate solvent, such as CH_2Cl_2. Treatment of compounds of formula **27** with chloroformates of formula **28**, which are generally commercially available or can be readily synthesized, in a suitable solvent, such as CH_2Cl_2, in the presence of a suitable base, such as triethylamine, affords compounds of formula (I). Similarly, compounds of formula **27** may be reacted with sulfonyl chlorides of formula **29**, which are generally commercially available or can readily be synthesized, in a suitable solvent, such as CH_2Cl_2, in the presence of a suitable base, such as triethylamine, to afford compounds of formula (I).

Scheme 10

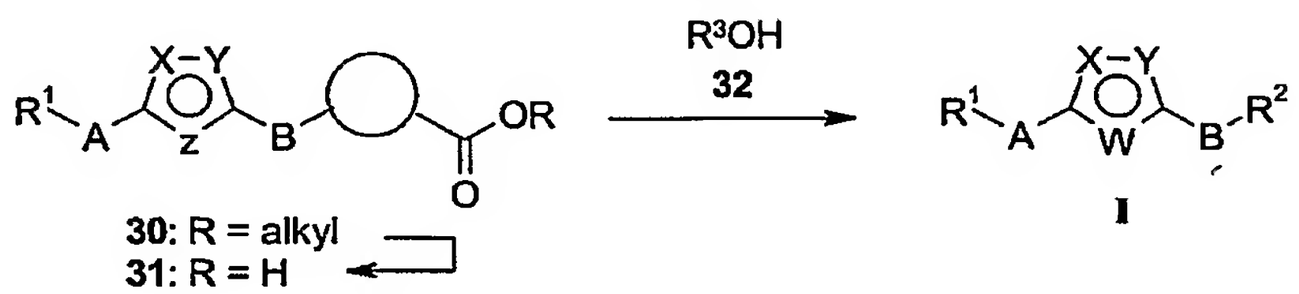


Compounds of formula (I) in which R^2 contains an amide group may be synthesized from compounds of formula **27** and a suitable acid (R^3COOH), or activated derivative thereof, in an amide bond forming reaction.

Compounds of formula (I) where R^2 contains an ester moiety may be synthesized as illustrated in Scheme 11. Compounds of formula **30** in which R is an alkyl group, for example a methyl group, may be synthesized using procedures described in Schemes 1-9. The alkyl group is firstly removed under appropriate conditions to afford compounds of formula **31**. For example, when R = Me compounds of formula **30** may be generated in the presence of a suitable base, for example LiOH, in a suitable solvent, such as water-methanol. The acids of formula **31** are then condensed with alcohols of formula **32**, which are commercially available or can be synthesized using known techniques. The condensation may be achieved by, for example, heating

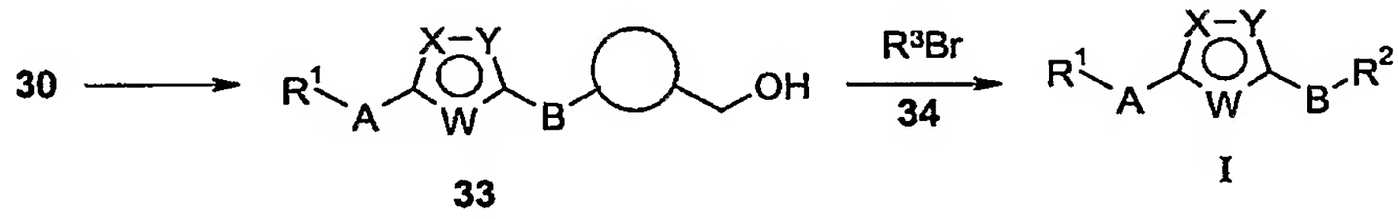
compounds of formula **31** with alcohols of formula **32** in the presence of thionyl chloride, giving rise to compounds of formula (I).

Scheme 11



Compounds of formula (I) where R^3 contains an ether group may also be synthesized from compounds of formula **30** as illustrated in Scheme 12. Compounds of formula **30** may be converted to the corresponding alcohol **33** by the action of a suitable reducing agent, for example diisobutylaluminium hydride, in a suitable solvent, such as CH_2Cl_2 and can then be treated firstly with a suitable base, such as sodium hydride, in a suitable solvent, such as THF, followed by an appropriate alkylating agent, such as an alkyl halide of formula **34** to afford compounds of formula (I).

Scheme 12



Compounds of formula (I) where B contains a NR^5 group where R^5 is hydrogen can be further transformed into compounds of formula (I) where R^5 is $C(O)R^7$, $S(O)_2R^8$, or an optionally substituted C_{1-4} alkyl group using standard techniques known to those with skill in the art for acylation, sulfonylation and reductive amination respectively.

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

As indicated above the compounds of formula (I) are useful as GPR116 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), including the compounds of provisos c) to e), in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPR116, as a regulators of satiety, e.g. resulting in the prophylactic or therapeutic treatment of obesity, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented

in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as

starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and

fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health,

sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I), including the compounds of provisos a) to e), may be used in the treatment of diseases or conditions in which GPR116 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which GPR116 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts and cardiovascular complications).

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I), including the compounds of provisos a) to e), or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I), including the compounds of provisos a) to e), may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-1 antagonists and CB-1 antagonists, amylin antagonists, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

Other diseases or conditions in which GPR116 has been suggested to play a role include those described in WO00/50562 and US 6,468,756, for example cardiovascular disorders, hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer's disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials and methods

Column chromatography was carried out on SiO_2 (40–63 mesh) unless specified otherwise.

LCMS data were obtained as follows: Atlantis 3μ C_{18} column (2.1 × 30.0mm, flow rate = 0.85ml/min) eluting with a H_2O–MeCN solution containing 0.1% HCO_2H over 6min with UV detection at 220nm. Gradient information: 0.0–0.3min 100% H_2O; 0.3–4.25 min: Ramp to 10% H_2O–90% CH_3CN; 4.25min–4.4min: Ramp to 100% CH_3CN; 4.4-4.9: Ramp to 10% (5% MeCN in H_2O)–90% MeCN; 3.8–4.4min: 4.4-4.9min: Hold at 100% MeCN; 4.9–6.0min: Return to 100% H_2O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES^+) ion or negative ion (ES^-) mode. Atmospheric Pressure Chemical Ionisation (APCI) spectra were obtained on a FinniganMat SSQ 7000C instrument.

^1H nmr spectra were recorded on a Varian Mercury 400 spectrometer, operating at 400 MHz. Chemical shifts are reported as ppm relative to tetramethylsilane (δ=0).

The syntheses of the following compounds have been reported previously:

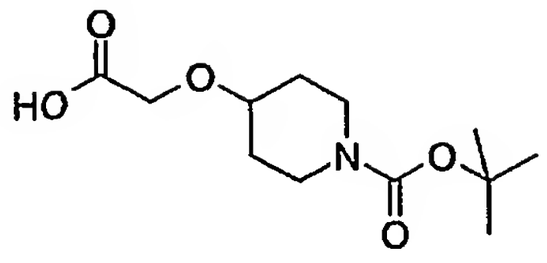
N-Hydroxyisonicotinamidine and *N*-hydroxynicotinamidine: A. R. Martin et al, J. Med. Chem., 2001, 44, 1560-1563;

N-Hydroxy-2-pyridin-3-yl-acetamidine and *N*-hydroxy-2-pyridin-4-yl-acetamidine: WO 01/047901;

4-Pentylcyclohexanecarbonitrile: J. C. Liang and J. O. Cross, Mol. Cryst. Liq. Cryst., 1986, 133, 235-244.

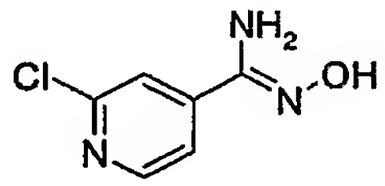
Abbreviations and acronyms: Ac: Acetyl; DMF: *N*,*N*-Dimethylformamide; Et: Ethyl; IH: Isohexane; RT: Retention time; rt: Room temperature; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran.

Preparation 1: 4-Carboxymethoxypiperidine-1-carboxylic acid, *tert*-butyl ester



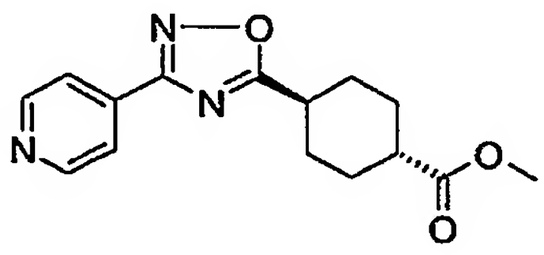
Sodium hydride (596mg of a 60% dispersion in oil, 14.9mmol) was added portionwise to a stirred solution of *tert*-butyl-4-hydroxypiperidine-1-carboxylate (1.0g, 5mmol) in anhydrous THF (20ml) at rt. After 15min, bromoacetic acid (1.38g, 9.94mmol) was introduced and stirring continued for 5h. Additional bromoacetic acid (5mmol) and sodium hydride (5mmol) were added and stirring continued for 24h. The reaction was quenched with water (2ml) and diluted with EtOAc (20ml), which was washed with saturated aqueous $NaHCO_3$ (20ml). Using dilute HCl, the aqueous phase was acidified to pH 2 and the precipitate extracted into EtOAc (50ml). The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (5%AcOH in IH-EtOAc, 7:3 to 1:1) to afford the title acid: RT = 2.89min; *m/z* (ES^+) = 260.3 $[M+H]^+$.

Preparation 2: 2-Chloro-*N*-hydroxyisonicotinamidine



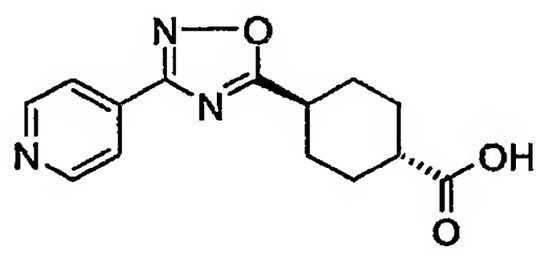
A solution of sodium carbonate (382mg, 3.61mmol) and $NH_2OH.HCl$ (502mg, 7.22mmol) in water (10ml) was added to 2-chloro-4-cyanopyridine (1.0g, 7.22mmol) and the mixture heated to 80°C. Sufficient ethanol (10ml) was then added to give a homogeneous solution. After 18h, the solution was cooled and the ethanol removed *in vacuo*. The solid precipitate was collected by filtration, washed with ethanol and CH_2Cl_2 and dried, affording the title compound: RT = 0.86min; *m/z* (ES^+) = 172.1 $[M+H]^+$.

Preparation 3: *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester



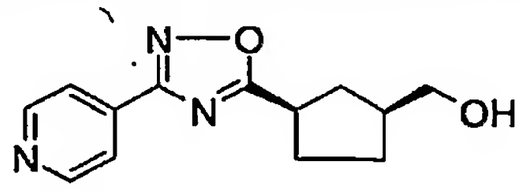
A solution of cyclohexane-1,4-dicarboxylic acid monomethyl ester (1.053g, 5.66mmol) and triethylamine (800μl, 5.66mmol) in toluene (30ml) was cooled to 0°C and isobutylchloroformate (735μl, 5.66mmol) and the mixture stirred at rt for 30min. Activated, powdered 3Å molecular sieves (5g) and *N*-hydroxyisonicotinamidine (705mg, 5.14mmol) were added and the mixture heated under reflux for 18h. On cooling, the mixture was filtered through Celite, the solvent removed *in vacuo* and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.20min; *m/z* (ES^+) = 288.2 $[M+H]^+$

Preparation 4: *trans*-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid



Water (0.5ml) and lithium hydroxide (9.2mg, 0.22mmol) were added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester (30mg, 0.104mmol) in THF (1.5ml). The mixture was heated at 60°C for 1.5h then cooled and the THF removed *in vacuo*. Water (5ml) was added, the aqueous washed with EtOAc (5ml) and carefully acidified with 1M HCl to pH 4. The resulting precipitate was extracted into 3% MeOH-EtOAc (2x15ml), the combined organic phases dried ($MgSO_4$) and evaporated to afford the title compound: RT = 2.74min, *m/z* (ES^+) = 274.2 $[M+H]^+$.

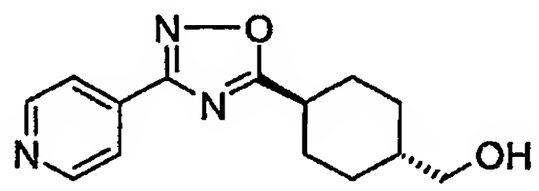
Preparation 5: *trans*-[3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol



Sodium hydride (100mg of a 60% dispersion in oil, 2.5mmol) was added to a solution of *N*-hydroxyisonicotinamidine (344mg, 2.5mmol) in THF and the mixture heated under reflux for 1h. Methyl-3-hydroxymethylcyclopentane-1-carboxylate (396mg, 2.5mmol) was added in one portion and heating was continued for 18h. After cooling the solution was filtered through celite and the filtrate concentrated *in vacuo*.

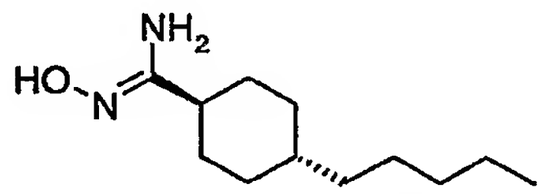
The residue was purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 2.59min, *m/z* (ES^+) = 246.1 $[M+H]^+$.

Preparation 6: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol



A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester in CH_2Cl_2 (13ml) was cooled to -30°C and diisobutylaluminium hydride (1.59ml of a 1M solution in toluene, 1.59mmol) introduced dropwise. After 30min the reaction was quenched with 2M HCl (6ml), the mixture warmed to rt and partitioned between 2M HCl (10ml) and CH_2Cl_2 (10ml). The aqueous phase was neutralised using 2M NaOH then extracted with CH_2Cl_2 (4x20ml). The combined organics were dried ($MgSO_4$) and evaporated to afford the title compound: RT = 2.59min, *m/z* (ES^+) = 260.2 $[M+H]^+$.

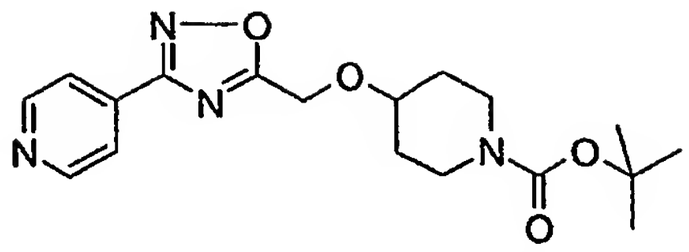
Preparation 7: *trans-N*-Hydroxy-4-pentylcyclohexylamidine



A solution of potassium carbonate (2.49g, 18mmol) and $NH_2OH.HCl$ (2.50g, 36mmol) in water (15ml) was added to 4-pentylcyclohexanecarbonitrile (4.30g, 24mmol) and the mixture heated to 80°C. Sufficient ethanol (approx. 45ml) was then added to give a homogeneous solution. After 10h the solution was cooled, diluted with water (200ml) and the solid material collected by filtration. The solid was dissolved in EtOAc (150ml), which was washed with brine (50ml) and dried ($MgSO_4$). The solvent was reduced in volume to 15 ml and hexane (60ml) added to precipitate the title compound, which was collected by filtration: RT = 2.86min; *m/z* (ES^+) = 213.2 $[M+H]^+$.

Example 1

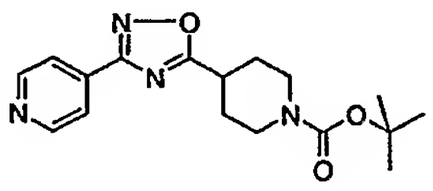
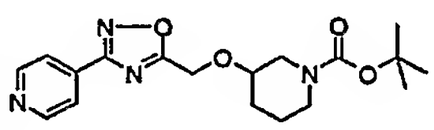
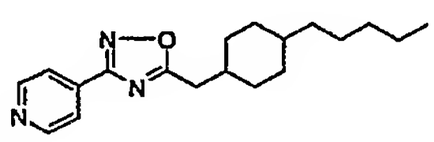
4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid, *tert*-butyl ester

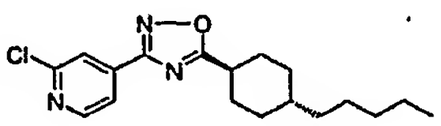
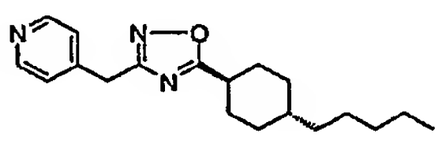
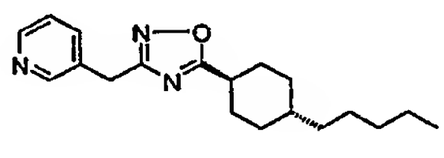
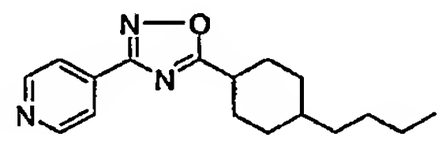
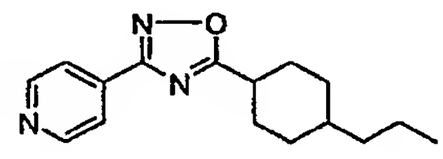
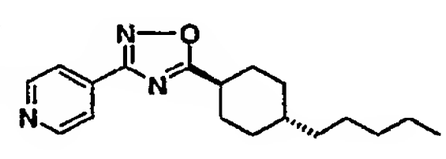


A stirred solution of triethylamine (123µl, 0.87mmol) and 4-carboxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (227mg, 0.87mmol) in toluene (10ml) was treated with isobutylchloroformate (113µl, 0.87mmol). After 20min, activated powdered 3Å molecular sieves (0.7g) and *N*-hydroxyisonicotinamidine (100mg, 0.73mmol) were added and the mixture heated under reflux for 18h. On cooling, the mixture was filtered through Celite, the solvent removed *in vacuo* and the residue purified by flash chromatography (IH-EtOAc, 35:65) to afford the title compound: RT = 3.29min; *m/z* (ES^+) 361.3 $[M+H]^+$; δ_H ($CDCl_3$) 1.40 (9H, s), 1.55-1.63 (2H, m), 1.80-1.92 (2H, m), 3.05-3.15 (2H, m), 3.64-3.79 (3H, m), 4.80 (2H, s), 7.90 (2H, d) and 8.75 (2H, d).

The [1,2,4]oxadiazoles in Table 1 were synthesised from the appropriate amidoxime with the corresponding acid, in a similar manner to that described in Example 1.

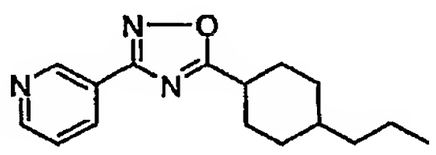
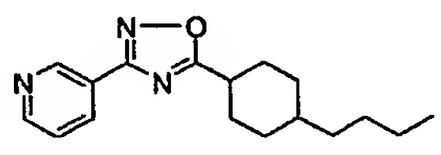
Table 1

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
2		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid, *tert*-butyl ester	3.52	331.3 $[M+H]^+$
3		3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid, *tert*-butyl ester	3.29	361.3 $[M+H]^+$
4		4-[5-(4-Pentylcyclohexylmethyl)-[1,2,4]oxadiazol-3-yl]pyridine	4.97	314.3 $[M+H]^+$

5		*trans*-2-Chloro-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine	5.19	334.3 $[M+H]^+$
6		*trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-ylmethyl]pyridine	3.77	314.3 $[M+H]^+$
7		*trans*-3-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-ylmethyl]pyridine	3.92	314.3 $[M+H]^+$
8		4-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine	4.69	286.2 $[M+H]^+$
9		4-[5-(4-*n*-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine	4.42	272.3 $[M+H]^+$
10		*trans*-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine	4.87	300.3 $[M+H]^+$

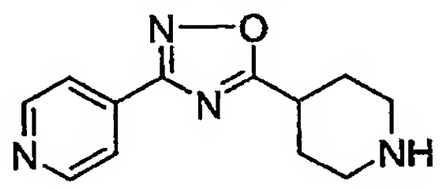
The compounds in Table 2 may also be prepared according to the method outlined in Example 1.

Table 2

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
11		3-[5-(4-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine	4.42	272.3 $[M+H]^+$
12		3-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine	4.76	286.3 $[M+H]^+$

Example 13

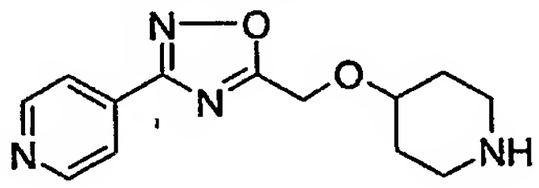
4-(5-Piperinin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine



Trifluoroacetic acid (20ml) was added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid, *tert*-butyl ester (1.64g, 4.96mmol) in CH_2Cl_2 (35ml). After 2.5h at rt, the solvent was evaporated under reduced pressure. The residual solid was suspended in EtOAc (150ml) and washed with saturated aqueous Na_2CO_3 (20ml). The aqueous was separated and extracted with EtOAc (3x30ml). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound (RT = 3.48min, *m/z* (ES^+) = 231.2 $[M+H]^+$).

Example 14

4-[5-(Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine

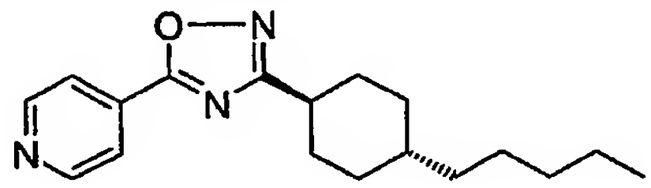


The *tert*-butoxycarbonyl group of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid, *tert*-butyl ester was removed using the

procedure described in Example 13 to afford the title compound: RT = 1.84min; *m/z* (ES^+) = 261.2 $[M+H]^+$.

Example 15

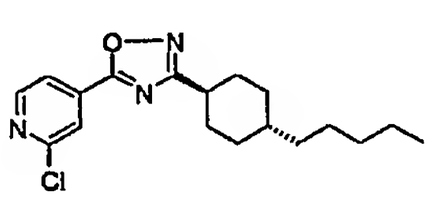
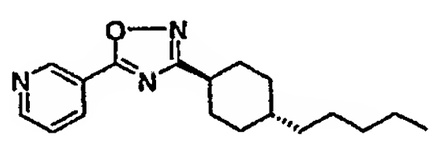
trans-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine

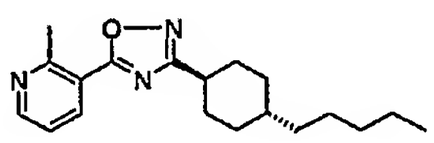
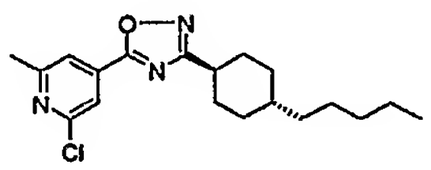
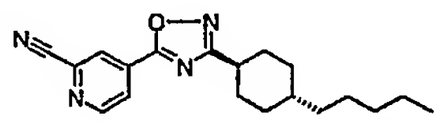
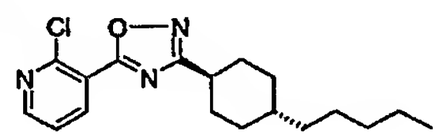
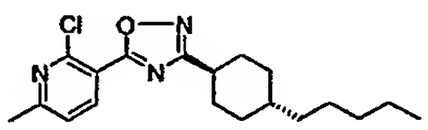
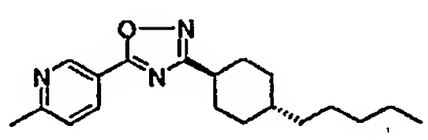
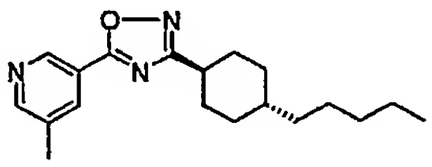
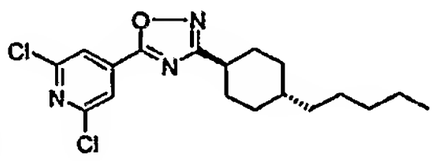


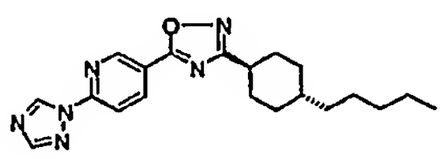
A solution of isonicotinic acid (36.2mg, 290μmol) and triethylamine (30mg, 290μmol) in anhydrous THF (3ml) was cooled to 0°C and isobutylchloroformate (39mg, 280μmol) was added. The mixture was stirred at rt for 1h and solid *N*-hydroxy-4-pentylcyclohexylamidine (50mg, 235μmol) added in one portion. After 45min, the reaction was diluted with EtOAc (12ml) and washed with saturated aqueous $NaHCO_3$ and brine (6ml), then dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in toluene (5 ml) and solution heated under gentle reflux for 2h. After evaporation to dryness, the residue was purified by flash chromatography (IH-EtOAc, 2:1) to afford the title compound: RT = 4.97min; *m/z* (ES^+) 300.3 $[M+H]^+$.

The [1,2,4]oxadiazoles in Table 3 were synthesised in a manner similar to that described in Example 15.

Table 3

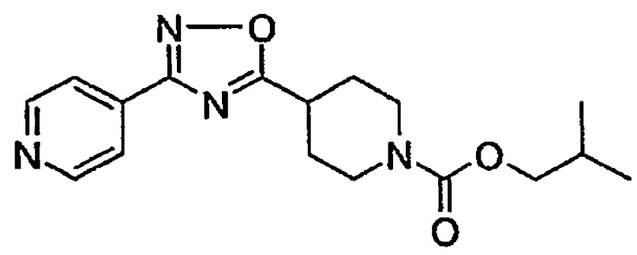
Ex	Structure	Name	RT (min)	*m/z* (ES^+)
16		*trans*-2-Chloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	5.14	334.3 $[M+H]^+$
17		*trans*-3-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	5.11	300.3 $[M+H]^+$

18		*trans*-2-Methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	4.92	314.3 $[M+H]^+$
19		*trans*-2-Chloro-6-methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl] pyridine	5.39	348.3 $[M+H]^+$
20		*trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile	4.91	366.4 $[M+CH_3CN]^+$
21		*trans*-2-Chloro-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	4.99	334.3 $[M+H]^+$
22		*trans*-2-Chloro-6-methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	5.34	348.3 $[M+H]^+$
23		*trans*-2-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	4.80	314.3 $[M+H]^+$
24		*trans*-3-Methyl-5-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	4.94	314.3 $[M+H]^+$
25		*trans*-2,6-Dichloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine	5.37	368.3 $[M+H]^+$

26		*trans*-5-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]-2-[1,2,4]triazol-1-ylpyridine	5.36	367.4 $[M+H]^+$

Example 27

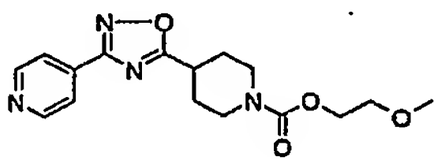
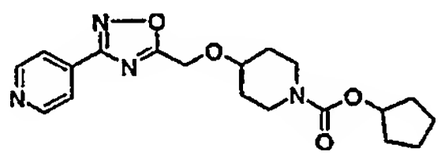
4-(3-Pyridin-4-yl-[1;2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid, isobutyl ester

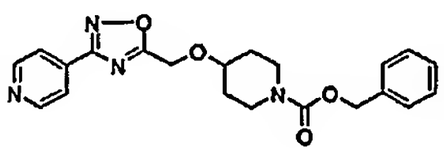
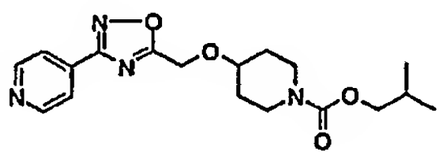
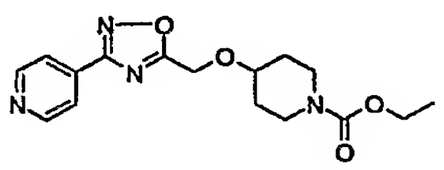


A solution of piperidine (18μL) and 4-(5-piperinin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (50mg, 0.22mmol) in CH_2Cl_2 (4ml) was treated with isobutylchloroformate (54mg, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 3.42min, *m/z* (ES^+) = 333.2 $[M+H]^+$.

Derivatisation of 4-[5-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl]pyridine (Example 14) with the appropriate chloroformate using the procedure described for Example 27 gave the examples in Table 4.

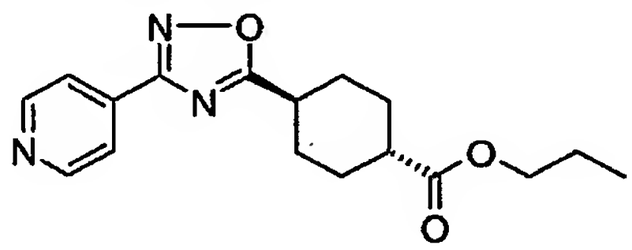
Table 4

Ex	Structure	Name	RT (min)	*m/z* (ES^+)
28		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid, 2-methoxyethyl ester	2.77	333.2 $[M+H]^+$
29		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester	3.51	373.4 $[M+H]^+$

30		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid benzyl ester	3.64	395.3 $[M+H]^+$
31		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)-piperidine-1-carboxylic acid isobutyl ester	3.49	361.3 $[M+H]^+$
32		4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid ethyl ester	3.03	333.3 $[M+H]^+$

Example 33

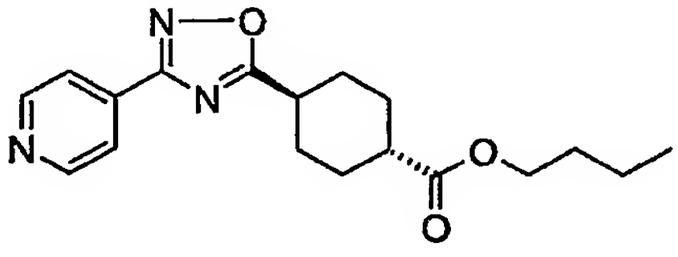
trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid propyl ester



Thionyl chloride (11.5μL, 0.1mmol) was added to a solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid in 1-propanol (2ml). The mixture was heated under reflux for 2h, cooled and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (10ml), washed with saturated aqueous $NaHCO_3$ (3ml) and brine (5ml), then dried ($MgSO_4$). Removal of the solvent afforded the title compound: RT = 3.67min, *m/z* (ES^+) = 316.3 $[M+H]^+$.

Example 34

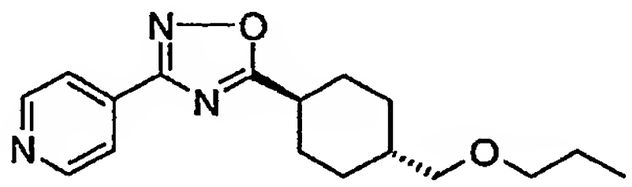
trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid butyl ester



A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid in 1-butanol was treated with thionyl chloride according to the method described in Example 33 to afford the title compound: RT = 3.92min, *m/z* (ES^+) = 330.3 $[M+H]^+$.

Example 35

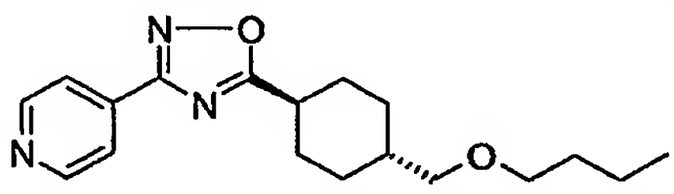
trans-4-[5-(4-Propoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol (50mg, 0.19mmol) in THF (2.5ml) was treated with sodium hydride (27mg of a 60% dispersion in oil, 0.68mmol) for 1h followed by 1-bromopropane (70µL, 0.77mmol) and tetrabutylammonium iodide (7mg, 19µmol). The mixture was stirred at rt for 72h, the solvent removed and the residue dissolved in CH_2Cl_2 (10ml). After washing with water (3ml), the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography (IH-EtOAc, 7:3) furnished the title compound: RT = 3.92min, *m/z* (ES^+) = 302.3 $[M+H]^+$.

Example 36

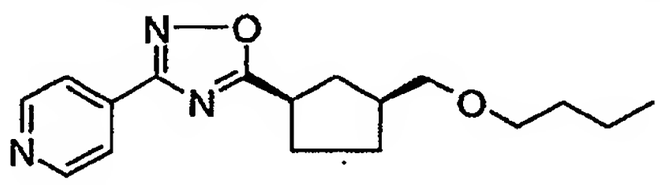
trans-4-[5-(4-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethanol in THF was treated with sodium hydride, 1-bromobutane and tetrabutylammonium iodide, as described for Example 35, to afford the title compound: RT = 4.16min, *m/z* (ES^+) = 316.3 $[M+H]^+$.

Example 37

cis-4-[5-(3-Butoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine

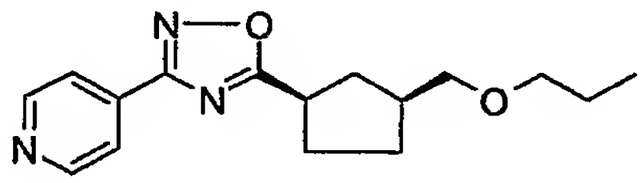


A solution of [3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol (40mg, 0.16mmol) in anhydrous THF (2ml) was treated with sodium hydride (23mg of

a 60% dispersion in oil, 0.57mmol) and tetrabutylammonium iodide (6mg, 16μmol). After stirring the mixture at rt for 10min, 1-bromobutane (59μL, 0.65mmol) was introduced and stirring continued for 72h. The solvent was removed *in vacuo*, the residue dissolved in CH_2Cl_2 (20ml) and washed with water (2x5ml). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography (IH-EtOAc, 7:3) afforded the title compound: RT = 3.99min, *m/z* (ES^+) = 302.3 $[M+H]^+$.

Example 38

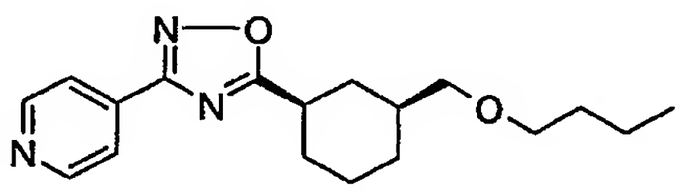
cis-4-[5-(3-Propoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine



[3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol was reacted with 1-bromopropane in the presence of tetrabutylammonium iodide using an analogous procedure to that described for Example 37 to afford the title compound: RT = 3.69min, *m/z* (ES^+) = 288.3 $[M+H]^+$.

Example 39

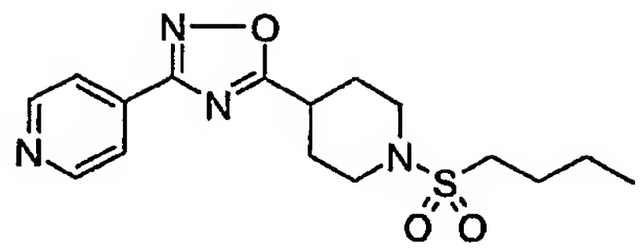
cis-4-[5-(3-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine



Methyl-3-hydroxymethylcyclohexane-1-carboxylate was reacted with *N*-hydroxy-isonicotinamidine, using the reaction conditions described in Preparation 5, to afford [3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexyl]methanol: RT = 2.70min, *m/z* (ES^+) = 246.1 $[M+H]^+$. This was subsequently alkylated with 1-bromobutane according to the procedure described in Example 37 to afford the title compound: RT = 4.11min, *m/z* (ES^+) = 316.3 $[M+H]^+$.

Example 40

4-{5-[1-(Butane-1-sulfonyl)piperidin-4-yl]-[1,2,4]oxadiazol-3-yl}pyridine



A solution of piperidine (18μl, 0.22mmol) and 4-(5-piperinin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (50mg, 0.22mmol) in CH_2Cl_2 (4ml) was treated with butane-1-sulfonyl chloride (56μl, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous $NaHCO_3$ (1ml). The organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was dissolved in EtOAc (5ml) and extracted into 2M HCl (10ml). The aqueous phase was then basified using 2M NaOH, and extracted with CH_2Cl_2 (2x10ml). The combined organic phases were dried ($MgSO_4$) and evaporated to afford the title compound: RT = 3.29min, *m/z* (ES^+) = 351.2 $[M+H]^+$.

The biological activity of the compounds of the invention may be tested in the following assay systems:

Yeast Reporter Assay

The yeast cell-based reporter assays have previously been described in the literature (e.g. see Miret J. J. et al, 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al, 1999, Bioorg. Med. Chem. Lett., 9:2413-2418; King K. et al, 1990, Science, 250:121-123); WO 99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPA1) has been deleted and replaced with G-protein chimeras constructed using multiple techniques. Additionally, the endogenous yeast alpha-cell GPCR, Ste3 has been deleted to allow for a homologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fus1. By placing β-galactosidase (LacZ) under the control of the Fus1 promoter (Fus1p), a system has been developed whereby receptor activation leads to an enzymatic read-out.

Yeast cells were transformed by an adaptation of the Lithium acetate method described by Agatep et.al. (Agatep R. et al, 1998, Transformation of Saccharomyces cerevisiae by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier).

Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10 μg), 2 μg of each of two Fus1p-LacZ reporter plasmids (one with URA selection marker and one with TRP), 2 μg of GPR116 (human or mouse receptor) in yeast expression vector (2μ origin of replication) and a lithium acetate/ polyethylene glycol/ TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60 min. The yeast cells were then heat-shocked at 42°C for 15 min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for β-galactosidase, yeast cells carrying the human or mouse GPR116 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells are still dividing and have not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90 μl of yeast cells are added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the β-galactosidase was added to each well. In these experiments, Fluorescein di (β-D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20 µl per well of 500µM FDG/2.5% Triton X100 was added (the detergent is necessary to render the cells permeable). After incubation of the cells with the substrate for 60 min, 20 µl per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without compound).

WHAT IS CLAIMED IS:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S;

A is $(CH_2)_n$;

B is $(CH_2)_n$, wherein one of the CH_2 groups is optionally replaced by O, NR^5, $S(O)_m$ or C(O);

n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

R^1 is 3- or 4-pyridyl or 4- or 5-pyrimidinyl any of which is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, aryl, OR^6, CN, NO_2, $S(O)_mR^6$, $CON(R^6)_2$, $N(R^6)_2$, $NR^{10}COR^6$, $NR^{10}SO_2R^6$, $SO_2N(R^6)$, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

R^2 is a 4- to 7-membered cycloalkyl substituted by R^3, $C(O)OR^3$, $C(O)R^3$ or $S(O)_2R^3$, or a 4- to 7-membered heterocyclyl containing one or two nitrogen atoms which are unsubstituted or substituted by $C(O)OR^4$, $C(O)R^3$ or $S(O)_2R^3$;

R^3 is C_{3-7} alkyl, C_{3-7} alkenyl or C_{3-7} alkynyl, wherein one of the CH_2 groups is optionally replaced by O, C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^4 is C_{2-7} alkyl, C_{2-7} alkenyl or C_{2-7} alkynyl wherein one of the CH_2 groups is optionally replaced by O, or C_{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4} alkylheterocyclyl or C_{1-4} alkylheteroaryl, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^5 is hydrogen, $C(O)R^7$, $S(O)_2R^8$ or C_{1-4} alkyl optionally substituted by OR^6, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups are optionally

substituted with one or more substituents selected from halo, C_{1-2} alkyl, C_{1-2} fluoroalkyl, OR^6, CN, $N(R^6)_2$ and NO_2;

R^6 are independently hydrogen, or C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocyclyl group or heteroaryl, wherein the cyclic groups are optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^9, CN, SO_2CH_2, $N(R^{10})_2$, and NO_2; or a group $N(R^{10})_2$ optionally forms a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR^{10};

R^7 is hydrogen, C_{1-4} alkyl, OR^6, $N(R^6)_2$, aryl or heteroaryl;

R^8 is C_{1-4} alkyl, C_{1-4} fluoroalkyl, aryl or heteroaryl;

R^9 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl; and

R^{10} is hydrogen or C_{1-4} alkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;

b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ^{t}butyl ester;

c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;

d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or

e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein n is independently 0, 1 or 2.

3. A compound of formula (I) as defined in any one of Examples 1, 3 to 7, 9 to 11 or 14 to 40, or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound according to claim 1, including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

5. A method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to claim 1, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

6. A method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to claim 1, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

7. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to claim 1, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

8. A method for the treatment of diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to claim 1, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

ABSTRACT OF THE DISCLOSURE

Compounds of formula (I):

$$R^1\text{-}A\text{-}V\text{-}B\text{-}R^2$$

(I)

or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.